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EXAMINER	
JEAN-LOUIS, SAMIRA JM	

ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
06/10/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/563,193	NEYSES, LUDWIG	
	Examiner	Art Unit	
	SAMIRA JEAN-LOUIS	1627	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 July 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-22* is/are rejected.

7)☒ Claim(s) *23-26* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Arguments

This Office Action is in response to the amendment submitted on 07/14/09. Claims 14-26 are currently pending in the application. Accordingly, claims 14-26 are being examined on the merits herein.

Receipt of the aforementioned amended claims is acknowledged and has been entered.

Applicant's argument with respect to the rejection of claim 23 under 35 U.S.C. 112, second paragraph has been fully considered. Given that applicant has amended claim 23, such rejection is now moot. Consequently, the rejection of claim 23 under 35 U.S.C. 112, second paragraph is hereby withdrawn.

Applicant's argument with respect to the rejection of claim 23 under 35 U.S.C. 112, first paragraph has been fully considered. Given that applicant has amended claim 23, such rejection is now moot. Consequently, the rejection of claim 23 under 35 U.S.C. 112, first paragraph is hereby withdrawn.

Applicant's argument with respect to the 103(a) rejection over Chaudhary in view of Wennemuth has been fully considered. Applicant argues that the instant invention is the first to demonstrate the expression of PMCA4 in sperm cells; infertility in PMCA4-

knockout mice; and direct suppression of sperm mobility by PMCA4 inhibitors in sperm along with comparative data supporting such statement. Moreover, applicant argues that Chaudhary teaches that PMCA1b is distinct from PMCA4 and would thus possess a contrasting conformation rigidity as a result of residue substitution and thus would not be expected to behave similarly as PMCA4 and second, Chaudhary fails to teach the particular PMCA isoform found in his tested cells and would thus make unclear to one of ordinary skilled in the art if binding of calcium is actually operating via another Ca2+ transporter. Such arguments are however not found persuasive as the Examiner respectfully points out that contrary to applicant's statement, the claims are not directed the expression of PMCA4 but rather to a method of achieving a contraceptive effect comprising administering a PMCA4 inhibitor. Thus, regardless of the expression levels of PMCA4, the limitations to be addressed involve achieving a contraceptive effect using a PMCA4 inhibitor. While applicant provided data regarding the effect of deletion of PMCA4 in mice cells, the Examiner maintains that Chaudhary in view of Wennemuth did indeed render obvious applicant's invention. Chaudhary teaches that plasma membrane pumps are present in all mammalian cells (i.e. inclusive of sperm cells, erythrocytes, etc..). Additionally, Chaudhary teaches that PM Ca2+ pumps are encoded by four PMCA genes that are alternatively spliced into PMCA1, PMCA2, PMCA3, and PMCA4 with PMCA1b being the most widely expressed. While their sequences are conserved, Chaudhary teaches that the first putative extracellular domain is not. However, when Chaudhary conducted his experiments PMCA4 only differed from PMCA1b by one residue. Importantly, Chaudhary teaches that Caloxin 2A1 was able to

inhibit PMCA1b but also produced a complete inhibition of plasma membrane ATPase in erythrocytes that expresses mainly PMCA4. As a result, Chaudhary suggests that Caloxin 2A1 would also inhibit **all of the PMCA isoforms.** While applicant argues that that PMCA1b is distinct from PMCA4, the Examiner contends that PMCA1b differs solely by one residue substitution and thus should not prevent caloxin from binding PMCA4. Additionally, the Examiner maintains that a single substitution does not necessarily signify a complete conformational change of PMCA4. Notwithstanding applicant's arguments, the Examiner contends Chaudhary demonstrated that Caloxin 2A1 was able to produce a complete inhibition (i.e. a high degree of inhibition which would suggest inhibition of various PMCA pumps) in a cell line that expresses mainly PMCA4 (see Chaudhary, pg. C1029, left col., last paragraph) thereby suggesting that caloxin 2A1 is also effective against PMCA4. In fact, Chaudhary explicitly states that caloxin 2A1 would inhibit all isoforms of PMCA (see Chaudhary, pg. C1029, left col., last paragraph). Consequently, the Examiner contends that one of ordinary skill in the art would have indeed found it obvious to try the use of Caloxin 2A1 to inhibit PMCA4 in any cell type in view of the disclosure of Chaudhary.

As for applicant's arguments that Chaudhary himself states that "one cannot rule out different affinities of Caloxin 2A1 for individual PMCA4 and thus not clear if such inhibitor would necessarily inhibit PMCA4, such arguments are not found persuasive as the Examiner contends that given that the claims are not directed to a particular amount of inhibition, differences in affinities would not result in lack of inhibition but rather in the degree of inhibition that would be exerted by Caloxin 2A1 on each PMCA isoform.

However, if applicant believes otherwise, it is incumbent upon applicant to demonstrate through side by side comparison that the suggestion of the prior art is fallible and would not result in any inhibition whatsoever. Moreover, the examiner contends that it would have been obvious to try such inhibitor since Chaudhary suggested that such inhibitor would inhibit all of the PMCA isoforms. As for applicant's arguments that applicant tested their experiments in sperm cells as opposed to erythrocytes and that Chaudhary never envisioned sperm cells as possessing PMCA pumps, the Examiner maintains that such arguments are not found persuasive as Chaudhary specifically teaches that plasma membrane (PM) Ca2+ pumps are found in all mammalian cells. Moreover, Wennemuth demonstrated the presence of PMCA pumps in sperm cells (See Wennemuth, fig. 2 and 3 and pg. 119). As a result, the Examiner contends that given that sperm cells express PMCA ATPase pumps and given the teaching of Chaudhary, one of ordinary skill in the art would have indeed found it obvious to try Caloxin 2A1 to inhibit PMCA4 in sperm cells. Consequently, the examiner maintains that the 103(a) rejection was indeed proper.

Applicant's argument with respect to the 103 (a) rejection over Wennemuth has been fully considered. Applicant argues that because Wennemuth teaches that PMCA and NCX Ca2+ pumps are taught to act in synergy, a skilled person would be unable to attribute Ca2+ clearance exclusively to PMCA channels. Such arguments are however not found persuasive as the Examiner contends that the instant claim as written do not exclude the presence of additional Ca2+ pumps. Moreover, the Examiner again refers

applicant to Wennemuth who clearly demonstrated that PMCA is indeed present in sperm cells. Thus, regardless if PMCA works in concert with other Ca2+ pumps, this is no way negates the involvement of PMCA in Ca2+ transport in sperm cells. Moreover, Wennemuth was provided to demonstrate the role of Ca2+ in regulating sperm motility, sperm capacitation and involvement in acrosome reaction (i.e. a reaction that occurs when the sperm enters the oocyte during fertilization). Thus, because Ca2+ plays a role in sperm motility and fertilization (as taught by Wennemuth) and is regulated by PMCA pumps and Chaudhary teaches that Caloxin 2A1 should inhibit all isoforms of PMCA pumps, one of ordinary skill in the art would have indeed found it obvious to try the Caloxin 2A1 of Chaudhary to inhibit sperm motility and thus fertilization with the reasonable expectation of achieving an effective contraceptive method.

As for applicant's arguments that Chaudhary and Wennemuth do not teach the use of sperm cells in their experiments, such arguments are not found persuasive as the Examiner again reiterates that Chaudhary states that PMCA pumps are found in all mammalian cells. Moreover, Wennemuth demonstrated that sperm cells do indeed possess PCMA pumps. Consequently, one of ordinary skill in the art would have found it obvious to try caloxin 2A1 to inhibit PMCA4 in sperm cells since Wennemuth teaches that sperm cells also possess PMCA pumps and in view of Chaudhary who teaches that caloxin 2A1 should inhibit all isoforms of PMCA. As for applicant's synergy argument, such argument is not found persuasive as the Examiner again reiterates the fact that the claims are not directed to total inhibition. Because binding of caloxin 2A1 leads to reduction in sperm motility, this would also meet the limitation of the claims. Moreover,

the Examiner respectfully points out that applicant is arguing features not previously presented. It is noted that the features upon which applicant relies (i.e., in a sperm cell) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Nonetheless, the Examiner maintains that it would have still been obvious to try caloxin 2A1 in sperm cells given the disclosures of Chaudhary and Wennemuth.

As for Zimmerman, it was provided to demonstrate that oral contraceptives are known to be administered in various forms and thus would have been well within the purview of the skilled artisan to formulate the PMCA4 inhibitor in oral, parenteral, or coated mechanical contraceptive form. Papurt, on the other hand, was provided to demonstrate that condoms are contraceptive devices well known in the art as mechanical barriers. Thus, to enhance contraceptive effects and prevent infections, one of ordinary skill in the art would have indeed found it obvious to add the use of condoms in the contraceptive method with the reasonable expectation of obtaining a method that is effective in preventing conception and effective in reducing infections. As a result, the Examiner maintains that the rejections over Zimmerman and Papurt do indeed render obvious applicant's invention.

For the foregoing reasons, the rejections under 35 U.S.C. 112 first and second paragraphs are withdrawn. The rejections under 35 U.S.C. 103(a) remain proper.

However, in view of applicant's amendment, the following objection and modified 103 (a) Final rejections are being made.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 14-15 and 17-20 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Chaudhary et al. (Am. J. Physiol Cell Physiol. 2001, Vol. 280, pgs. C1027-C1030, previously cited) in view of Wennemuth et al. (J. Gen. Physiol. June 30, 2003, Vol. 122, pgs. 115-128, previously cited).

Chaudhary et al. teach that plasma membrane (PM) Ca2+ pump is a Ca2+ Mg2+-ATPase that expels Ca2+ from cells to help them maintain low concentrations of cytosolic Ca2+ (see abstract). Additionally, Chaudhary et al. teach that the PM calcium pumps use the energy of hydrolysis of ATP to expel cellular Ca2+ (see pg. C1027, left col., Introduction section). Moreover, Chaudhary et al. teach that the PM Ca2+ pumps are present in all mammalian cells (i.e. inclusive of sperm cells) thereby suggesting that such pumps are also present in humans as well (see pg. C1027, left col., Introduction Section). Specifically, Chaudhary et al. teach that PM Ca2+ pumps are encoded by four

PM Ca2+-ATPase genes (a.k.a. PMCA) whose sequences are conserved in the various isoforms (pg. C1027, right col.). Furthermore, Chaudhary et al. teach that the sequence of extracellular domain 401-413 in human PMCA1b is similar to the corresponding sequences in PMCA 4 and thus supporting the notion that the PMCA inhibitor of Chaudhary et al. should also inhibit PMCA4 (see pg. C1029, left col. Discussion Section, last paragraph). Particularly, Chaudhary et al. teach Caloxin 2A1 as a novel PM Ca2+ pump inhibitor selected for biding to the extracellular domain of PMCA (see abstract and pg. C1029, right col., paragraph 1). Chaudhary et al. teach that Caloxin 2A1 was dissolved in Krebs solution (i.e. carrier) which contains 115 mM NaCl, 5 mM KCl, 22 mM NaHC93, 1.7 mM CaCl2, 1.1 mM MgCl2, 1.1 kH2Po4, 0.3 mM EDTA, and 7.7 mM glucose (instant claim 20; see pg. C1028, left col., Contractility experiments, last paragraph).

Chaudhary et al. however do not specifically teach a method achieving contraceptive effect comprising a PMCA4 isoform inhibitor or a method for diagnosing infertility in a human male. Similarly, Chaudhary et al. do not teach that the PMCA4 inhibitor is performed as a single contraceptive event or as a repeated contraceptive event in sperm cells.

Wennemuth et al. teach that the spermatozoon is specialized for a single vital role in fertilization (see abstract). In fact, past studies show that Ca2+ signals produced by the opening of PM membrane channels initiate several events required for the sperm

to reach and enter the egg but reveal little about how resting Ca2+ is maintained or restored after elevation (see abstract). This suggests that blocking such PM channels should prevent fertilization as inhibition of such PM channels would prevent the sperm from reaching the egg and thereby block fertilization. Importantly, Wennemuth et al. teach that the Ca2+ ATPase pump of the PM (PMCA) performs the major task of Ca2+ clearance (see abstract and pg. 120, right col., last paragraph). Additionally, Wennemuth et al. teach that like other excitable cells, mammalian spermatozoa (i.e. including human sperm; instant claims 18-19) possess multiple voltage-gated calcium channels and use Ca2+ signals to control physiological responses (see pg. 115, left col., Introduction). Particularly, Wennemuth et al. teach that calcium is considered a regulator of sperm motility, a participant in capacitation, and an essential second messenger for the acrosome reaction (i.e. a reaction that occurs when sperm is penetrating the layers of the oocyte during fertilization; see pg. 115, left col.). According to Wennemuth et al., the sperm PM depolarizes, Ca2+ channels open, Ca2+ enters, and the Ca2+-dependent acrosome reaction ensues (see pg. 115, left col.). Wennemuth et al. teach that four major Ca2+ clearance mechanisms exist in most animal cells including PMCA which exports cytoplasmic Ca2+ ion and imports one or two extracellular protons at the expense of ATP (see pg. 115, right col., paragraph 2). Additionally, Wennemuth et al. teach that carboxyeosin (instant claim 15) was used in blocking PMCA in sperm cells but prevented the cells from KCL depolarization (see pg. 120, right col., top paragraph). Thus, inhibition of PMCA would necessarily result in a

contraceptive effect as the acrosome reaction (i.e. sperm penetrating the egg or ovum) would necessarily be prevented (instant claim 14).

Thus, to one of ordinary skill in the art at the time of the invention would have found it obvious to utilize Caloxin 2A1 to inhibit sperm PM since Wennemuth et al. teach that the Ca2+ PM pump is involved in the fertilization of human eggs by sperms. Moreover, one of ordinary skill in the art would have found it obvious to utilize the PMCA4 inhibitor caloxin 2A1 as either a single contraceptive event or as a repeated contraceptive event depending on the efficacy of the method as a contraceptive method. Thus, given the teachings of Chaudhary and Wennemuth, one of ordinary skill would have been motivated to utilize Caloxin 2A1 to inhibit PMCA4 inhibitor in sperm cells with the reasonable expectation of providing a method that is effective in preventing conception and effective in inhibiting fertilization.

Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Chaudhary et al. (Am. J. Physiol Cell Physiol. 2001, Vol. 280, pgs. C1027-C1030, previously cited) in view of Wennemuth et al. (J. Gen. Physiol. June 30, 2003, Vol. 122, pgs. 115-128, previously cited) as applied to claims 14-15 and 17-20 above and in further view of Zimmerman et al. (U.S. 2002/0164368).

The Chaudhary and Wennemuth references are as discussed above and incorporated by reference herein. However, Chaudhary and Wennemuth do not teach oral, parenteral or coated mechanical contraceptive of the PMCA inhibitors.

Zimmerman teaches male contraceptive composition that can be administered orally (see abstract). Zimmerman also teaches that oral contraceptives are the most prominent chemical contraceptive agents; however, other chemical agents can be used in the form of creams, foams, gels and suppositories (see pg. 1, paragraphs 0003 and 0008). Of interest, Zimmerman demonstrated that contraceptive compositions can be made in various forms including oral, parenteral, or topical administration (see pg. 5, paragraphs 0060-0062).

Thus, to one of ordinary skill in the art at the time of the invention would have found it obvious to formulate the PMCA4 inhibitor composition of Chaudhary since Zimmerman teaches that contraceptive composition can be formulate as an oral, parenteral or topical application. Thus, given the teachings of Chaudhary, Wennemuth, and Zimmerman, one of ordinary skill would have been motivated to formulate the composition of the aforementioned method as an oral, parenteral, or topical formulation in view of the disclosure of Zimmerman with the reasonable expectation of providing a contraceptive method that can be easily administered.

Claims 21-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chaudhary et al. (Am. J. Physiol Cell Physiol. 2001, Vol. 280, pgs. C1027-C1030, previously cited, previously submitted) in view of Wennemuth et al. (J. Gen. Physiol. June 30, 2003, Vol. 122, pgs. 115-128, previously submitted) as applied to claims 14-15 and 17-20 above and in further view of Papurt (U.S. 5,314,447, previously cited).

The Chaudhary and Wennemuth references are as discussed above and incorporated by reference herein. However, Chaudhary and Wennemuth do not teach addition of conventional contraceptive device.

Papurt teaches the use of condoms and contraceptive devices as mechanical barriers (see abstract). Papurt further teach that condom barrier prophylactic devices and barrier contraceptive devices are generally known in the overall population, as well as the art, for their ability to prevent conception (i.e. a contraceptive product; col. 1, lines 17-20). According to Papurt, the more common types, involved male condoms or so-called female condoms positioned in such a way prior to sexual contact (see col. 1, lines 27-31). Moreover, Papurt teaches that condoms are known historically and have been in existence for centuries (see col. 1, lines 66-67 and col. 2, lines 17).

Thus, to one of ordinary skill in the art at the time of the invention would have found it obvious to further add the use of condom to the modified contraceptive method

of Chaudhary since Papurt teaches the effective use of condom for preventing conception. Thus, given the teachings of Chaudhary and Wennemuth, one of ordinary skill would have been motivated to add condoms to the contraceptive regimen of Chaudhary with the reasonable expectation of providing an enhanced contraceptive method that is not only effective in preventing conception but also effective against possible infections.

Objections

Claims 23-26 are objected to because of the following informalities: Claims are dependent upon rejected claims. Applicant is required to incorporate all of the limitations of claim 14 into claim 23. Appropriate correction is required.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samira Jean-Louis whose telephone number is 571-270-3503. The examiner can normally be reached on 7:30-6 PM EST M-Th.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/S. J. L. /

Examiner, Art Unit 1627

06/03/2010

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1627